REMARKS

Information Disclosure Statement

1. On the copy of sheet 2 of the May 16, 2005 IDS Form returned with the previous Office Action of July 29, 2008, the Examiner drew a line through JP 2726672. However, JP 2726672 should have been considered and made of record, since it is a related family member of USP 4,952,581. The Examiner is therefore respectfully requested to return to the undersigned a copy of sheet 2 of the May 16, 2005 IDS Form, with the Examiner's initials next to each cited publication, including JP 2726672.

2. For the reasons set forth in the attached INFORMATION DISCLOSURE STATEMENT, the Examiner is respectfully requested to return to the undersigned a copy of the September 5, 2007 IDS Form with an indication thereon that the cited publication (which included an English-language abstract) was considered and made of record.

Presently Claimed Invention

Applicants' present claim 1 is directed to a therapeutic composition for treating glaucoma comprising a combination of pharmaceutically effective amounts of drugs comprising (i) a Rho

kinase inhibitor selected from the group consisting of (R)-trans-N-(pyridin-4-yl)-4-(1-aminoethyl)cyclohexane carboxamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, 1-(5-isoquinolinesulfonyl)-homopiperazine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, or a salt or an ester thereof and (ii) a prostaglandin selected from the group consisting of isopropyl unoprostone, latanoprost, travoprost and bimatoprost, or a salt or ester thereof, and optionally a pharmaceutically acceptable carrier.

Applicants' present claim 2 concerns a therapeutic composition for treating glaucoma which comprises a combination of pharmaceutically effective amounts of drugs comprising (i) a Rho kinase inhibitor selected from the group consisting of (R)-trans-N-(pyridin-4-yl)-4-(1-aminoethyl)cyclohexane carboxamide, (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridin-4-yl)-4-(1-aminoethyl)benzamide, 1-(5-isoquinolinesulfonyl)-homopiperazine and 1-(5-isoquinolinesulfonyl)-2-methylpiperazine, or a salt or an ester thereof and a (ii) prostaglandin selected from the group consisting of isopropyl unoprostone, latanoprost, travoprost and bimatoprost, or a salt or an ester thereof, wherein the actions of the Rho kinase inhibitor and the

prostaglandin are complemented and/or enhanced by each other, and optionally a pharmaceutically acceptable carrier.

Obviousness Rejection Under 35 USC 103

Claims 1, 2 and 21 were rejected under 35 USC 103 as being unpatentable over EP 286903 ("Bito") in view of USP 7,015,210 to Aiken, P. Vasantha Rao et al., *Modulation of Aqueous Humor Outflow Facility by the Rho Kinase-Specific Inhibitor Y-27632,* 42 INV. OPHTHALMOL. VIS. SCI., 1029 (April 2001) and USP 6,271,224 to Kapin et al. for the reasons set forth in the previous Office Actions of January 12, 2009 and July 29, 2008, and for the reasons set forth in item no. 3 on pages 2 to 5 of the January 5, 2010 Office Action.

It was admitted in the previous Office Actions of July 29, 2008 and January 12, 2009 that Bito, Aiken and Rao et al. describe different methods of treating glaucoma using prostaglandins and Rho inhibitors.

It was admitted in the January 5, 2010 Office Action that Bito (i) does not specifically recite any of applicants' claimed prostaglandins and (ii) does not specify Rho-kinase inhibitors as effective combined therapeutics.

Applicants' Rebuttal of the Obviousness Rejection

Bito et al. is directed to the use of a prostaglandin in combination with an adrenergic blocking agent for reduction of intraocular pressure (see the title of Bito et al.).

Aiken is directed to a method for treating or preventing ophthalmic disorders by reducing intraocular pressure comprising the administration of one or more aldosterone receptor antagonists that contain a 9,11-epoxy moiety (see the Abstract of Aiken). As an optional further ingredient, Aiken mentions a prostaglandin (see claim 2 of Aiken).

It is evident that Bito et al. and Aiken are being relied upon only for their disclosures of prostaglandins.

Clearly, Bito et al. and Aiken considered that the administration of a prostaglandin by itself was insufficient to effectively reduce intraocular pressure, so both Bito et al. and Aiken employed other drugs, namely an andrenergic blocking agent in Bito et al., and an aldosterone receptor antagonist containing a 9,11-epoxy moiety in Aiken. These other drugs employed by Bito et al. and Aiken are not recited in applicants' claims. Bito et al. and Aiken do not teach or suggest a Rho inhibitor as recited in applicants' present claims.

Rao et al. is directed to a Rho kinase-specific inhibitor Y-27632. Rao et al. do not teach or suggest combining such Rho kinase-specific inhibitor Y-27632 with a prostaglandin as recited in applicants' present claims.

Kapin et al. disclose a method of treating glaucoma by administering an isoquinolinesulfonyl compound (see the Abstract of Kapin et al.). Kapin et al. do not teach or suggest the specific combination of drugs as recited in applicants' present claims.

The January 5, 2010 Office Action neglected to address the serious potential difficulty when using plural drugs, namely, the possible serious drug-drug interactions. The combining of drugs is thus vastly different than the combining of non-drug chemical compounds, for example, detergents.

The obviousness rejection is based on the ground that it would have been obvious for one having ordinary skill in the art to combine and use two or three drugs having actions of reducing intraocular pressure, based on the four cited references. However, none of the four cited references (alone or combined) teach or suggest the specific combination of compounds recited in applicants' present

claims, nor describe the significant unexpected (synergistic) results achieved by the combination of drugs recited in applicants' present claims.

Thus, it is respectfully submitted that one of ordinary skill in the art would not consider to combine the four cited references as set forth in the January 5, 2010 Office Action to attempt to arrive at the presently claimed invention. Moreover, assuming *arguendo* that the four cited references were combinable, it is respectfully submitted that one having ordinary skill in the art would not arrive at the presently claimed invention or the unexpected results afforded by the presently claimed invention by the combination of the four cited references.

As discussed hereinbelow, the presently claimed invention is further patentable based on the unexpected results set forth in the present specification.

The Examiner's attention is directed to the pharmacological test data in Fig. 2 of the present application. Fig. 2 is reproduced as follows:

Fig. 2

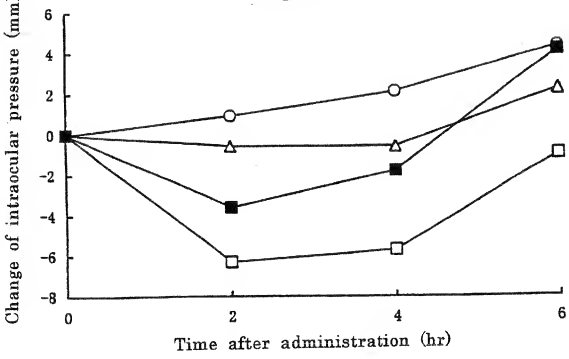

Change of intraocular pressure (mmHg)
6
4
2
0
-2
-4
-6
-8
0
2
4
6
Time after administration (hr)

Fig. 2 shows that intraocular pressure changes of a control group (○) and a group of Compound B (1-(5-isoquinolinesulfonyl)homopiperazine dihydrochloride) alone, (■) 6 hours after administration are almost the same. This indicates that the pharmacological effect of Compound B has been exhausted and no longer exhibits an intraocular pressure reducing effect.

In other words, when Compound B and isopropyl unoprostone are administered in combination, if the effects are merely additive, the intraocular pressure reduction of the concurrently administered group (□) of Compound B and isopropyl unoprostone, 6 hours after administration should show the same value as that of isopropyl unoprostone alone (△) (i.e., the pharmacological effect of the group of Compound B (■) has been already exhausted).

However, despite the pharmacological effect of the group of Compound B (■) being exhausted, the intraocular pressure reduction of the concurrently administered group (□) of Compound B and isopropyl unoprostone actually shows a much larger value (about 3 mmHg) than that of isopropyl unoprostone alone (△).

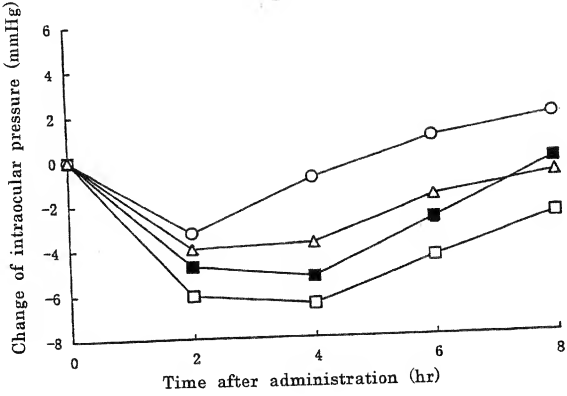
Stated differently, Fig. 2 shows that the concurrent administration of Compound B and isopropyl unoprostone (according to the presently claimed invention) brings about a synergistic result, which far exceeds a mere addition (additive effect) of the amount of intraocular pressure reduction when Compound B and isopropyl unoprostone are administered separately.

The same can be said for 8 hours after administration in Fig. 3 of the present application, and 6 and/or 8 hours after administration in Fig. 4 of the present application. Fig. 3 is directed to the combined administration of latanoprost and Compound A ((R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)-benzamide dihydrochloride). Fig. 4 is directed to the combined administration of latanoprost and said Compound B.

Furthermore, since each intraocular pressure changes 8 hours after administration in Fig. 1 and each intraocular pressure reduction 4 hours after administration in Fig. 2, shows a similar tendency, it can be said that Fig. 1 shows a similar tendency as Fig. 2.

Figs. 1, 3 and 4 of the present application are reproduced as follows:

Fig. 1



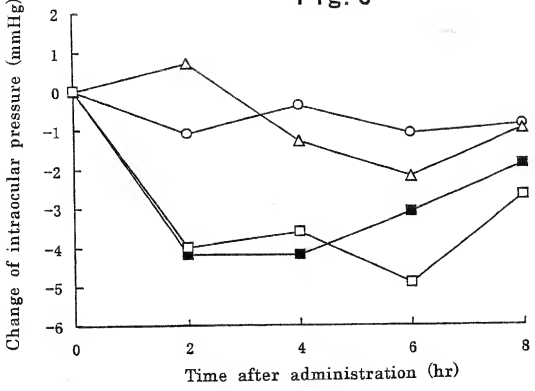
□ represents Compound A + isopropyl unoprostone

■ represents only Compound A

△ represents only isopropyl unoprostone

○ represents a control group

Fig. 3



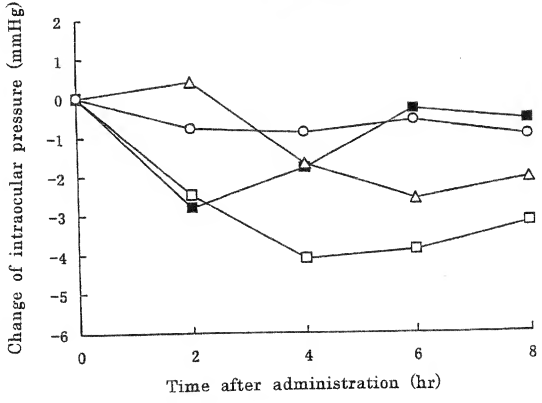
□ represents Compound A + latanoprost

■ represents only Compound A

△ represents only latanoprost

○ represents a control group

Fig. 4



□ represents Compound B + latanoprost

■ represents only Compound B

△ represents only latanoprost

○ represents a control group

As stated above, none of the four cited references (alone or combined) disclose or suggest the specific combination of compounds recited in applicants' present claims, nor describe the significant unexpected (synergistic) results achieved by such combination. Such significant unexpected results afforded by applicants' presently claimed invention by far exceeds the effect when the compounds are individually administered. Thus, it is respectfully submitted that the presently claimed invention patentably distinguishes over the four cited references, individually, or combined in the manner as set forth in the Office Action.

Withdrawal of the 35 USC 103 rejection is therefore respectfully requested.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the

undersigned at the telephone number given below for prompt action.

Respectfully submitted,

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Encs.: (1) PETITION FOR EXTENSION OF TIME
(2) INFORMATION DISCLOSURE STATEMENT